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Abstract: While high levels of glucocorticoids are generally neuro-damaging, a related adrenal steroid, dehydroepiandrosterone (DHEA), has anti-glucocorticoid and neuroprotective properties. Previous work has shown increased circulating levels of DHEA and abnormal cortisol/DHEA ratios in people with schizophrenia, however reports are limited and their relationship to neuropathology is unclear. We performed the largest study to date to compare levels of serum DHEA and cortisol/DHEA ratios in people with schizophrenia and healthy controls, and investigated the extent to which cortisol/DHEA ratios predict brain volume. Serum cortisol and DHEA were assayed in 94 people with schizophrenia and 81 healthy controls. T1-weighted high-resolution anatomical scans were obtained using a 3 T Achieva scanner on a subset of 59 people with schizophrenia and 60 healthy controls. Imaging data were preprocessed and analyzed using SPM12. People with schizophrenia had significantly increased serum DHEA levels ($p = 0.002$), decreased cortisol/DHEA ratios ($p = 0.02$) and no difference in cortisol levels compared to healthy controls. Cortisol/DHEA ratios were inversely correlated with hippocampal ($r = -0.33$ $p = 0.01$) and dorsolateral prefrontal cortex ($r = -0.30$, $p = 0.02$) volumes in patients. Our findings suggest that the cortisol/DHEA ratio may be a molecular blood signature of hippocampal and cortical damage. These results further implicate the role of DHEA and hypothalamic-pituitary-adrenal axis dysfunction in the pathophysiology of schizophrenia.

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Cortisol-dehydroepiandrosterone ratios are inversely associated with hippocampal and prefrontal brain volume in schizophrenia

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ABSTRACT

While high levels of glucocorticoids are generally neuro-damaging, a related adrenal steroid, dehydroepiandrosterone (DHEA), has anti-glucocorticoid and neuroprotective properties. Previous work has shown increased circulating levels of DHEA and abnormal cortisol/DHEA ratios in people with schizophrenia, however reports are limited and their relationship to neuropathology is unclear. We performed the largest study to date to compare levels of serum DHEA and cortisol/DHEA ratios in people with schizophrenia and healthy controls, and investigated the extent to which cortisol/DHEA ratios predict brain volume. Serum cortisol and DHEA were assayed in 94 people with schizophrenia and 81 healthy controls. T1-weighted high-resolution anatomical scans were obtained using a 3 T Achieva scanner on a subset of 59 people with schizophrenia and 60 healthy controls. Imaging data were preprocessed and analyzed using SPM12. People with schizophrenia had significantly increased serum DHEA levels ($p = 0.002$), decreased cortisol/DHEA ratios ($p = 0.02$) and no difference in cortisol levels compared to healthy controls. Cortisol/DHEA ratios were inversely correlated with hippocampal ($r = -0.33$ $p = 0.01$) and dorsolateral prefrontal cortex ($r = -0.30$, $p = 0.02$) volumes in patients. Our findings suggest that the cortisol/DHEA ratio may be a molecular blood signature of hippocampal and cortical damage. These results further implicate the role of DHEA and hypothalamic-pituitary-adrenal axis dysfunction in the pathophysiology of schizophrenia.

1. Introduction

Clinical and biological data indicate impaired biological response to stress in people with schizophrenia (Walker and Diforio, 1997), which is associated with dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (Ciufolini et al., 2014) and alterations in cortical stress response molecules (Sinclair et al., 2011; Webster et al., 2002). High levels of glucocorticoids induce neurotoxicity, atrophy, inhibition of neurogenesis and neuronal death (Sapolsky et al., 1985). Increased corticosteroids are associated with structural changes (usually decreased volume) in the hippocampus (Sapolsky et al., 1990) and prefrontal cortex (Carrion et al., 2010). The hippocampus and prefrontal cortex are principal targets for glucocorticoids where molecular abnormalities in glucocorticoid responses have been identified in individuals with schizophrenia (Sinclair et al., 2011; Webster et al., 2002) and where brain volume reductions have been repeatedly reported (Gur et al., 2000; Nelson et al., 1998). Circulating glucocorticoids, such as cortisol, have been linked to hippocampal volumetric reductions in people with first episode psychosis, demonstrating the deleterious effects of stress early in the illness (Mondelli et al., 2010b).

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Studies of cortisol alone do not take into account the role of other regulatory hormones in the HPA axis in mediating or attenuating the adverse effects of glucocorticoids. In humans, cortisol and dehydroepiandrosterone (DHEA) are co-synthesized and released by the adrenal glands via adrenocorticotropic hormone stimulation in response to stress. DHEA has multiple neuroprotective effects on the central nervous system. DHEA protects neurons against glutamate and beta amyloid-protein toxicity (Cardounel et al., 1999) and against insults resulting from oxidative stress (Bastianetto et al., 1999). DHEA enhances myelination and synaptogenesis, and stimulates the growth of neurons in the central nervous system (Friess et al., 2000). DHEA readily crosses the blood-brain barrier and levels of DHEA in the blood and cerebrospinal fluid (CSF) are strongly correlated (Kancheva et al., 2011), thus changes in circulating levels of DHEA may be especially pertinent to brain health. Studies have generally reported increased levels of DHEA in individuals with schizophrenia relative to healthy people (di Michele et al. 2005; Ritsner et al., 2006; Strous et al., 2004), although decreased DHEA (Tourney and Hatfield, 1972) and no difference in (Ritsner et al., 2004) DHEA levels have also been found. Despite varying reports regarding circulating levels, owing to its properties, it is speculated that DHEA serves as a protective or compensatory mechanism in the disease (Strous et al., 2004). In support of this, there is evidence for an inverse relationship between levels of DHEA-sulfate and symptom severity (depressive and negative symptoms) early on in the disease (Garner et al., 2011), although this relationship was not found in chronically ill people with schizophrenia (Ritsner et al., 2004).

Owing to the anti-glucocorticoid properties of DHEA, the cortisol/DHEA ratio has been considered an indicator of the functional state of HPA axis activity and may therefore be more informative than the absolute concentrations of either cortisol or DHEA alone (Wolkowitz et al., 2001). Previous research suggests that the ratio of cortisol/DHEA found in the peripheral blood may be increased in people with schizophrenia (Ritsner et al., 2004), however some studies have found no difference in the cortisol/DHEA ratio compared to healthy people (Gallagher et al., 2007; Garner et al., 2011). There are findings that cortisol/DHEA-sulfate ratios are positively correlated with positive and negative symptoms (Garner et al., 2011) as well as with depressive symptoms (Garner et al., 2011; Ritsner et al., 2004) in schizophrenia. The finding of a relationship between cortisol/DHEA-sulfate and negative symptom severity in people with first-episode psychosis suggests that illness chronicity and antipsychotics may not be contributing factors in the relationship (Garner et al., 2011). While previous studies have assessed the relationship of cortisol/DHEA ratio to behavioral phenotypes, no study to date has investigated whether cortisol/DHEA ratios are associated with underlying biological changes such as neuroanatomical abnormalities. As the co-release of cortisol and DHEA in response to acute stress protects cells against the damaging effects of hypercortisolemia, the cortisol/DHEA ratio may be useful in examining stress-induced morphological changes in the brain.

Thus, the aims of the present study were, firstly, to compare serum cortisol, DHEA levels and cortisol/DHEA ratios in people with schizophrenia and healthy controls and, secondly, to examine whether the latter index predicts brain volume. We selected the hippocampus and prefrontal cortex as regions of interests (ROI) for our brain volume analysis as they are vulnerable targets of stress (Carrion et al., 2010; Mondelli et al., 2010b; Sapolsky et al., 1990) and regulate negative feedback of the HPA axis via their glucocorticoid receptors (Diorio et al., 1993; Jacobson and Sapolsky, 1991). On the basis of studies suggesting that DHEA may play a compensatory role in schizophrenia (di Michele et al., 2005; Strous et al., 2004), we hypothesized that patients in our study would display increased circulating levels of DHEA compared to controls. However, due to cortisol variation in schizophrenia (both upregulation and downregulation/blunted response due to HPA axis abnormalities (Jansen et al., 2000; Mondelli et al., 2010a)), our comparative analysis of serum cortisol and cortisol/DHEA ratios in schizophrenia patients versus healthy people was exploratory and therefore, we had a non-directional hypothesis concerning a potential direction of change. Lastly, we predicted that the cortisol/DHEA ratio would be negatively correlated with brain volume in people with schizophrenia, such that increased DHEA would buffer against the negative effects (e.g. brain atrophy) of chronic stress.

2. Materials and Methods

2.1. Participants

Ninety-four outpatients with schizophrenia or schizoaffective disorder and 81 healthy controls 18-51 years of age were included in the present study and were recruited to one of two sites: Sydney (Neuroscience Research Australia in Sydney, NSW, Australia) or Adelaide (Lyell McEwen Hospital in Adelaide, Australia). Patients were recruited from local clinics and via a national television program on schizophrenia research. Diagnoses were confirmed by clinical interview by a psychiatrist or psychologist using the Structured Clinical Interview for DSM-IV. All patients had been receiving antipsychotics for at least 1 year before their entry into the study (see Table S1 for numbers of patients receiving a single antipsychotic or a combination). Patients with a concurrent Axis I diagnosis, head injuries with loss of consciousness, seizures, recent history of alcohol and/or substance abuse/dependence (within past 5 years), a central nervous system infection, uncontrolled diabetes or hypertension, structural brain abnormalities, mental retardation or a learning disability were excluded. Additionally, females were excluded if they were currently pregnant or if they were receiving hormone therapy and refused alternate forms of birth control. Symptom severity in participants with schizophrenia was evaluated with the Positive and Negative Syndrome Scale (PANSS). Positive, negative, general psychopathology and total symptom severity scores were calculated. Inter-rater reliability was established with an average intraclass correlation coefficient of 0.90. Healthy control subjects were recruited through advertising. Healthy people with a personal history or first-degree relative with DSM-IV Axis I psychiatric diagnosis, history of a head injury with loss of consciousness, seizures, recent history of alcohol and/or substance abuse/dependence (within the past 5 years), a central nervous system infection, uncontrolled diabetes or hypertension, structural brain abnormalities, mental retardation or a learning disability were excluded. All participants were assessed with a four subtest version of the Wechsler Adult Intelligence scale, 3rd edition (WAIS-III) comprised of the Arithmetic, Digit Symbol, Similarities and Picture Completion subtests as an estimate of current IQ.

The protocol was approved by the Human Research Ethics Committees from the University of New South Wales and the South Eastern Sydney and Illawarra Area Health Service in Sydney, and the Queen Elizabeth Hospital, Adelaide, South Australia. All subjects provided written informed consent prior to participation in this study.

2.2. Serum collection and laboratory analyses

Fasting peripheral blood was collected from participants between 0900 and 1100 h to control for alternations in hormone levels due to circadian variations. Blood samples were put on ice and stored at −80 °C until assayed. Serum cortisol levels were assayed by South Eastern Area Laboratory Services in Randwick, NSW, Australia using a chemiluminescent immunometric assay (Siemens Immulite 2000). Serum DHEA levels were analyzed by the ANZAC Research Institute, Concord Hospital, NSW, Australia with liquid chromatography–mass spectrometry (LC-MS) analysis (Harwood and Handelsman, 2009). The limits of detection for assays were 27.6 nmol/L for cortisol and 0.05 ng/ml for DHEA. The intra-assay coefficients of variations were $< 10\%$. DHEA was converted to nmol/L to standardize units of measurement prior to computing cortisol/DHEA ratios.

2.3. Structural MRI acquisition and processing

Only a subset of participants received magnetic resonance imaging (MRI) scans (n = 121, Sydney site only). Structural MRI scans were acquired using a 3-Tesla Phillips Achieva scanner with an 8-channel bird-cage type head coil at Neuroscience Research Australia, Randwick, NSW, Australia. Each participant received a T1-weighted high-resolution anatomical scan (TR: 5.4 ms; TE: 2.4 ms; FOV: 256 mm; matrix: 256 × 256; sagittal plane; slice thickness: 1 mm, no gap; 180 slices).

All scans were processed and analysed using the VBM8 toolbox (http://www.neuro.uni-jena.de/vbm) implemented in Statistical Parametric Mapping software (SPM12; http://www.fil.ion.ucl.ac.uk/spm) running under MATLAB version 2012b. The T1-weighted images were segmented into tissue classes of grey matter, white matter and cerebrospinal fluid. Following this, a high-dimensional DARTEL normalization was performed for optimal registration of individual segments to a group mean template. The voxel-based morphometry analysis was restricted to differences in grey matter; therefore, the resulting grey matter volume segments were modulated by the Jacobian determinants to correct for local volume changes introduced by normalization. Finally, the DARTEL-normalized modulated grey matter segments were smoothed using an 8 mm full-width at half-maximum Gaussian kernel. Homogeneity using covariance was performed on the entire sample to help identify outliers, followed by visual inspection for artifacts, which resulted in the removal of two participants' scans, yielding a total of 60 healthy controls and 59 patients who were included in imaging analyses.

The hippocampus and prefrontal cortex were chosen as our two *a priori* regions of interest (ROI), for comparative and correlational analyses. An ROI mask of the bilateral hippocampus was created and defined by the Automated Anatomic Labelling system in WFU PickAtlas, dilated x1. An ROI mask of the bilateral DLPFC was created by combining Brodmann areas 9 and 46 using WFU PickAtlas (http://fmri.wfubmc.edu/software/pickatlas), dilated x1. The masks created in WFU Pick Atlas were resliced from the default 2 × 2x2 voxel dimension to 1.5 × 1.5 × 1.5 voxels in order to match the dimension of DARTEL-processed images. Using the segmented, normalized and modulated images, ROI grey matter volumes were obtained using get_totals.m Matlab script (Ged Ridgway; http://www0.cs.ucl.ac.uk/staff/g.ridgway/vbm/get_totals.m) with a signal threshold ≥ 0.1. Total intracranial volume (TIV), which was used as a covariate, was calculated by adding up the native space volumes of the grey matter, white matter and cerebrospinal maps using the Tissue Volumes tool.

2.4. Data Analysis

Antipsychotic dose was converted to mean daily chlorpromazine (CPZ) equivalent dose based on standard guidelines (Woods, 2003). Group differences between healthy controls and patients in relation to continuous demographic variables were assessed using 2-sample *t*-tests (2-tailed) and differences in categorical variables were determined using Chi-squared tests. Raw DHEA, cortisol and cortisol/DHEA values were normalized through log10 transformation and no outliers were detected (> 3 standard deviations from mean). Using partial correlations with age as a covariate, we determined whether DHEA and cortisol levels were correlated in diagnostic groups, separately, and determined whether antipsychotic dose was associated with DHEA levels in patients. We assessed whether age of onset was related to DHEA or cortisol/DHEA levels using Pearson's correlations and assessed whether duration of illness was related to DHEA or cortisol/DHEA using partial correlations, controlling for age. We also performed partial correlations in 83 patients, while controlling for age, between body mass index (BMI), as an indicator of metabolic syndrome (Fisher et al., 2019), and hormones, based on the observations that (1) the prevalence of metabolic syndrome is higher among individuals with schizophrenia as compared with healthy individuals (De Hert et al., 2009), (2) the prevalence of metabolic syndrome increases following antipsychotic use (Mitchell et al., 2013), (3) steroid hormones may regulate metabolic syndrome (Regelson and Kalimi, 1994), and (4) DHEA-sulfate serum levels are related to metabolic syndrome in acutely psychotic females (Boiko et al., 2020).

Our first aim was to compare serum cortisol, DHEA, and cortisol/DHEA ratios between people with schizophrenia and healthy controls while controlling for potential confounders (age and sex). For our initial model, we entered each hormone and their ratio as dependent variables in separate linear mixed models using the *lme4* package (Bates et al. (2015)) in R (R Core Team, 2017) including fixed effects for diagnosis (healthy control/schizophrenia), age, sex, an interaction of sex x diagnosis and random intercepts for each site (Sydney/Adelaide): $Hormone_i$ = Intercept + β_1*Diagnosis + β_2*Age + β_3*Sex + β_4*Sex*Diagnosis + random effect (site). To assess whether similar findings exist within the subset of participants from the Sydney site who underwent scanning, we also compared hormone levels between this subset of patients and controls.

Our second aim was to determine the extent to which cortisol/DHEA ratios predict brain volume. In SPM12, we compared brain volumes between patients and controls, restricted to the hippocampus and DLPFC using explicit masks, with age and TIV as nuisance parameters. Results were generated using a family-wise error rate (FWE) correction with a $p < 0.05$ at the cluster-level. Hippocampal and DLPFC volumes were used in partial correlation analyses with cortisol, DHEA and cortisol/DHEA ratios in controls and patients separately, while covarying for age. Pearson's correlations were performed between mean daily CPZ equivalent dose and ROI volumes to investigate the potential effects of antipsychotics on brain tissue changes.

3. Results

Regarding the overall sample, demographics of patients and controls and clinical characteristics of patients are presented in Table 1. The patients showed mild to moderate symptom severity based on the PANSS scores. There was a significant difference in age and expected significant differences in education and IQ between groups in which healthy controls were slightly younger (by ~4 years), received more

Table 1
Demographic Variables and Characteristics of the Whole Sample.

	Controls (*n* = 81) Mean (SD)	*Schizophrenia* (*n* = 94) Mean (SD)	t/ X^2	p-value
Age (years)	31.8 (8.4)	35.7 (8.5)	3.0	0.003
Education (years)	14.6 (2.2)	12.4 (2.3)	6.5	< 0.001
Sex (number)			2.2	0.14
Male	41	58		
Female	40	36		
Ethnicity (number)			5.4	0.25
Caucasian	65	81		
Asian	10	5		
Caucasian-Asian	2	5		
Other	4	2		
WAIS-III FSIQ	107.3 (14.9)	91.0 (12.7)	7.8	< 0.001
Age of onset (years)		22. 7 (5.6)		
Illness duration (years)		13.0 (7.6)		
Daily CPZ equivalents (mg)		555.5 (470.0)		
PANSS positive		15.0 (4.7)		
PANSS negative		14.3 (6.2)		
PANSS general		30.7 (8.9)		
PANSS total		60.0 (16.9)		

Abbreviations: CPZ, chlorpromazine; F, Female; M, male; PANSS, Positive and Negative Syndrome Scale; WAIS-III FSIQ, Wechsler Adult Intelligence Scale III full-scale IQ estimate

years of education and had a higher (by 16 points) estimated IQ score relative to patients. There were no significant differences in relation to the sex or ethnicity ratios between the groups.

Demographics of the subset of participants included in MRI analyses are presented in Table S2. Similar to the whole sample of 94 patients and 81 controls, we found significant differences in age and education such that scanned controls were on average ~4.5 years younger than scanned patients, received more years of education and had a higher IQ (by 17 points), and we found that the individuals in the subsample did not differ on any demographic, symptomatic or hormonal values as compared the total sample.

Neither sex nor sex x diagnosis interaction were significant predictors of any hormones (all $p > 0.1$), while we found significant effects of age on serum DHEA, cortisol and cortisol/DHEA ($p < 0.001$, $p = 0.006$, $p = 0.009$, respectively). Consequently, we used age as a covariate in all analyses related to hormones and our final model was as follows: $\text{Hormone}_i = \text{Intercept} + \beta_1\text{*Diagnosis} + \beta_2\text{*Age} + \text{random effect (site)}$.

3.1. Elevated DHEA levels and decreased cortisol/DHEA ratios in people with schizophrenia

Linear mixed models revealed significantly elevated serum DHEA levels in patients relative to healthy controls ($t = 3.13$, $df = 171.3$, $p = 0.002$, $R^2 = 0.17$), see Fig. 1. There was no significant difference in serum cortisol levels between diagnostic groups ($t = 0.63$, $df = 172.0$, $p = 0.53$, $R^2 = 04$). Cortisol/DHEA ratios were significantly decreased in people with schizophrenia as compared with healthy controls ($t = 2.47$, $df = 171.2$, $p = 0.02$, $R^2 = 0.12$).

Serum cortisol and DHEA levels were positively correlated in healthy controls ($r = 0.23$, $p = 0.04$) and were even more significantly and positively correlated in patients with schizophrenia ($r = 0.43$, $p < 0.001$). DHEA levels were not related to mean daily CPZ equivalents dose ($r = -0.06$, $p = 0.55$) in patients. Age of onset was not associated with DHEA ($r = -0.07$, $p = 0.50$) or cortisol/DHEA ($r = 0.13$, $p = 0.22$). Likewise, illness duration was not associated with DHEA ($r = -0.18$, $p = 0.08$) or cortisol/DHEA, controlling for age ($r = 0.04$, $p = 0.73$). Patients' BMI was not associated with their serum DHEA ($r = -0.01$, $p = 0.94$) or cortisol ($r = -0.13$, $p = 0.23$) levels.

Within the subsample of participants who underwent MRI scanning, we also found that patients displayed significantly elevated serum DHEA levels ($t = 3.03$, $p = 0.003$) and decreased cortisol/DHEA ($t = 1.96$, $p = 0.05$) compared to healthy controls.

3.2. Cortisol/DHEA ratios are negatively correlated with brain volume in patients

People with schizophrenia showed significant grey matter volume reductions relative to healthy controls in the hippocampus and DLPFC, FWE corrected at $p < 0.05$ (see Table S3). Cortisol/DHEA ratios were significantly, negatively correlated with hippocampal ($r = -0.33$, $p = 0.01$, $df = 56$) and DLPFC ($r = -0.30$, $p = 0.02$, $df = 56$) volume in patients (see Fig. 2). In contrast, cortisol/DHEA ratios showed no significant correlations with hippocampal ($r = -.01$, $p = 0.93$, $df = 57$) or DLPFC ($r = -.08$, $p = 0.54$, $df = 57$) volume in healthy controls. There was a near-significant positive correlation ($r = 0.26$, $p = 0.05$, $df = 56$) between DHEA and hippocampal volume in patients. There were no significant correlations between ROI volumes and serum cortisol or DHEA levels alone in either group (Table S4). Mean daily CPZ equivalent dose was not associated with brain volume of either ROI (hippocampus: $r = -0.05$, $p = 0.73$; DLPFC: $r = -0.12$, $p = 0.36$).

4. Discussion

The key findings from the present study include: (1) significantly elevated serum DHEA levels in patients relative to controls; (2) significantly decreased cortisol/DHEA ratios in patients relative to controls; and (3) significant inverse relationships of cortisol/DHEA ratios to hippocampal and DLPFC volumes in patients after adjustment for age. Although it was not a primary aim of the present study, we also replicated well-established reports of hippocampal and DLPFC volume reduction in people with schizophrenia (Nelson et al., 1998; Selemon et al., 2002).

Our finding of elevated DHEA levels in the patient cohort is in agreement with other studies measuring DHEA in the periphery (di Michele et al., 2005; Ritsner et al., 2006; Strous et al., 2004) and in postmortem brain tissue (Marx et al., 2006) in people with schizophrenia. One study reported higher levels of DHEA-sulfate at first onset of psychosis but not in subsequent episodes (Beyazyüz et al., 2014), so they speculated that DHEA(S) levels diminish with chronic illness. However, we found significantly elevated DHEA levels in people with chronic schizophrenia who have had the illness for over a decade on average, indicating longstanding upregulation of DHEA, which is in support of other reports of elevated DHEA in chronically ill patients (di Michele et al., 2005). As DHEA levels are also elevated in drug-naive patients (Beyazyüz et al., 2014), this suggests that increased DHEA is related to pathology and not merely a result of antipsychotic use. To support this, we did not find a relationship between mean daily CPZ equivalent dose and DHEA levels. However, a recent study found that levels of DHEA-sulfate and cortisol differ between patients with and without metabolic syndrome (Boiko et al., 2020), which has been linked to antipsychotics (Mitchell et al., 2013). Although we did not find any relationships of BMI to cortisol or DHEA in our patient sample, we did not measure DHEA-sulfate in particular and cannot rule out the possibility that changes in hormones levels may in part reveal changes in metabolic-related activity known to occur in chronically ill patients receiving antipsychotics for long periods of time. Our measurement of hormones at a single-time point may be influenced by other

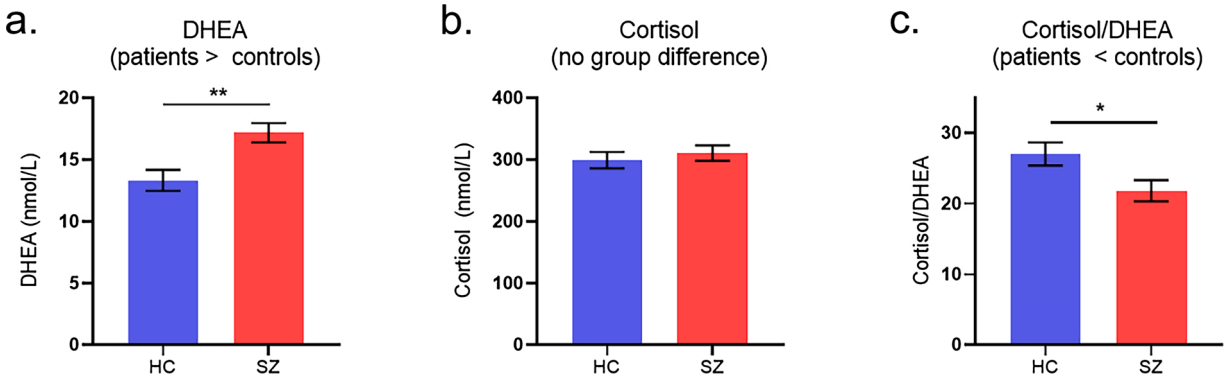

Fig. 1. Patients with schizophrenia displayed (a) significantly increased serum DHEA, (b) no difference in circulating cortisol levels, and (c) significantly decreased cortisol/DHEA ratios as compared with healthy controls. Plots reflect raw, age-adjusted means and standard error. (*$p < 0.05$, **$p < 0.01$)

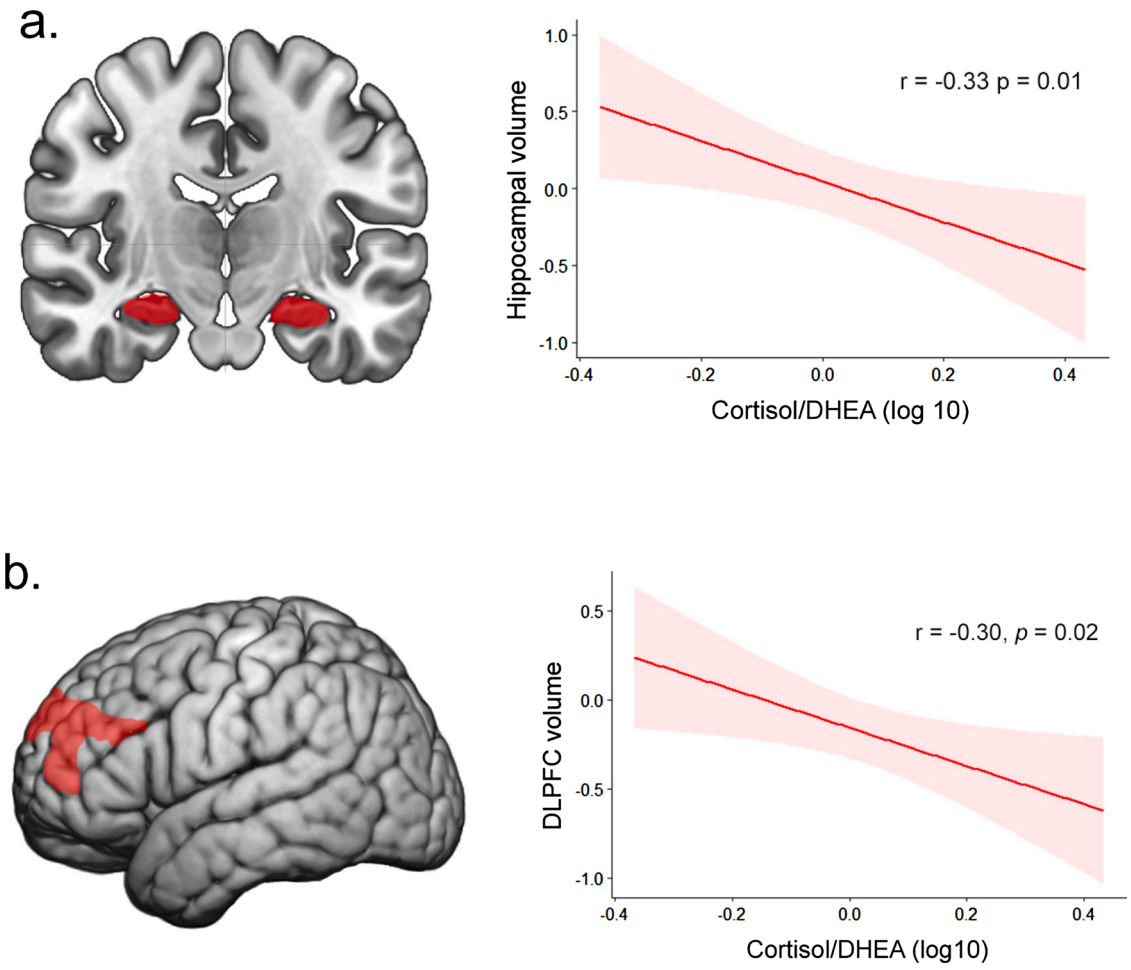

Fig. 2. Cortisol/DHEA ratios were significantly, negatively correlated with bilateral (a) hippocampal and (b) DLPFC volume in patients. The 95% confidence interval of the regression line is shaded in pink. Plots are residual plots, covarying for age.

stress-related (e.g. chronic stress related to schizophrenia and acute stress attributed to blood draw) and non-stress related (e.g. time of blood drawn relative to wake time, physical activity, number of hours slept, iatrogenic effects) factors (Chida and Steptoe, 2009; Hucklebridge et al., 2005). Repeated measures of hormones as opposed to a single measurement, in addition to assessments (e.g., how stressed the participant feels about having their blood drawn, lifetime exposure to stressful events, etc.), would help pinpoint potential contributors of stress more precisely.

DHEA may exert some of its actions through conversion into its potent sex steroid metabolites (i.e. estrogen and testosterone) and activation of androgen or estrogen receptors (Chen et al., 2005). In relation to this, downstream abnormalities in sex steroids could have implications for DHEA. Indeed, low circulating levels of testosterone have been found in men with schizophrenia (Misiak et al., 2018), which may initiate a positive feedback loop, prompting increased production of DHEA. While differences in DHEA's metabolites have been reported in schizophrenia patients varying by sex (e.g. with decreased testosterone in male patients (Misiak et al., 2018; Owens et al., 2018) and increased testosterone in female patients (Misiak et al., 2018)), it is unclear if sex also plays a moderating role in circulating DHEA in people with schizophrenia. In healthy individuals, previous evidence suggests that serum DHEA levels fluctuate in a non-linear manner with age differentially in males and females (Sulcová et al., 1997). One study has reported decreased serum levels of DHEA in only males with schizophrenia (Huang et al., 2017). Although we did not find significant effects of sex in our sample, future studies assessing how sex may influence DHEA and cortisol/DHEA levels in people with schizophrenia across the lifespan are warranted.

Our finding of decreased cortisol/DHEA ratios in people with schizophrenia is counter to one report of increased (Ritsner et al., 2004) and findings of no difference (Gallagher et al., 2007; Garner et al., 2011) in cortisol/DHEA ratios in patients. The combination of our findings - increased DHEA levels, a positive correlation between DHEA and cortisol reflecting DHEA-related anti-glucocorticoid activity, and the absence of hypercortisolemia - may suggest that in addition to cortisol, other factors are maintaining DHEA upregulation in schizophrenia, resulting in a low cortisol/DHEA ratio relative to controls. Increased DHEA may remain in circulation as a compensatory consequence of chronic stressors such as oxidative stress and increased inflammation in the body and brain, which are strongly implicated in schizophrenia (Fillman et al., 2013; Flatow et al., 2013). Oxidative damage has been found in the hippocampus (Che et al., 2010) and DLPFC (Gawryluk et al., 2011) in individuals with schizophrenia. Furthermore, administration of agents known to induce oxidative stress results in increased DHEA formation in the brain (Brown et al., 2003) and periphery (Rammouz et al., 2011). Therefore, our finding of elevated peripheral DHEA may also be indicative of an attempt at neuroprotection against oxidative stressors in people with schizophrenia. Our group has reported that IL-1β, IL-6 and IL-8 mRNA are upregulated in the DLPFC and periphery, within a subset of people with schizophrenia (Fillman et al., 2013; Fillman et al., 2016). DHEA decreases pro-inflammatory cytokine production *in vivo* (Kimura et al., 1998) and *in vitro* (Straub et al., 1998); therefore, increased DHEA levels in schizophrenia may represent an

increase in anti-inflammatory processes and reflect the body's effort to protect against inflammation. Another possible mechanism contributing to lower cortisol/DHEA ratios is a blunted cortisol response to stress, which has been found in people with schizophrenia by multiple groups (Jansen et al., 2000). Reduced production of cortisol or the preferential production of one hormone over the other could account for our finding of decreased cortisol/DHEA ratios in the schizophrenia group. On the whole, owing to the neuroprotective properties of DHEA, our results support the hypothesis that higher levels of DHEA in schizophrenia could reflect a compensatory upregulation against multiple factors and, similarly, that decreased cortisol/DHEA ratios relative to controls may reflect prolonged upregulation of a neuroprotective response and/or blunted cortisol response.

Importantly, as both increased DHEA and decreased cortisol/DHEA ratios have been found in people with post-traumatic stress disorder (Yehuda et al., 2006), findings from our study may not reflect schizophrenia-specific biomarkers per se, but instead demonstrate that deviations from normal HPA axis activity can be captured across diverse stress-related conditions. Although we measured levels of hormones as markers of HPA activation in the blood, the clinical relevance of our findings may depend upon the likelihood that the peripheral levels mirror the levels of these hormones in the brain. We have previously found parallel transcriptional changes in stress responsive genes in the brain and blood. In particular, reduced glucocorticoid receptor mRNA (Sinclair et al., 2012a; Sinclair et al., 2011; Sinclair et al., 2012b; Webster et al., 2002) and increased FKBP5 mRNA (Lee et al., 2019; Sinclair et al., 2013), which likely relates to greater stress levels or repeated stress exposure (Matosin et al., 2018), are found in schizophrenia. Indeed, changes in the stress responsive genes occur at the mRNA and protein level in the blood and in multiple brain regions in people with schizophrenia, suggesting that changes in stress-responsive genes may be widespread and systemic. Both cortisol and DHEA can cross the blood-brain barrier and studies have found that, across individuals within studies, cortisol in CSF correlates with circulating cortisol levels ($r = 0.89$, $p < 0.001$) (Carroll et al., 1976) and DHEA in CSF correlates with serum DHEA levels ($r = 0.65$, $p < 0.01$) (Guazzo et al., 1996). However, we must also consider that while the blood-brain barrier is selectively permeable to steroid hormones via transmembrane diffusion, the ease at which they penetrate may be dependent on the level and effectiveness of hormone carrier proteins (Mason et al., 2010; Pardridge and Mietus, 1979). Collectively, these lines of evidence enable us to make inferences on brain hormone levels based on blood markers, at least to some degree, and suggest that measurement of hormone transporters in brain endothelial cells may be of interest.

Previous studies examining cortisol and DHEA in schizophrenia have only assessed behavioral clinical phenotypes. This study is the first to report a relationship between cortisol/DHEA ratios and brain volume reductions in people with schizophrenia. We should consider the implications of our parallel, yet seemingly opposed, findings in patients of (1) an inverse relationship between cortisol/DHEA and brain volume and (2) decreased cortisol/DHEA compared to controls. It is not intuitive as to why elevated cortisol/DHEA ratios relate to reduced brain volume in patients, while patients have lower ratios and smaller brain volume relative to the controls. One explanation may be that the hormone levels in each diagnostic group are influenced by different biological processes such that the comparisons of the ratios across diagnostic groups is not linear. For example, it may be that baseline regulation of cortisol and DHEA differ in patients versus controls. Low/normal cortisol levels in patients may reflect blunting of the cortisol response due to adaptation of the HPA axis from extended periods of stress (Bunea et al., 2017); whereas, low/normal cortisol in healthy controls who experience less stress could relate to better regulation of cortisol. In patients, greater lifetime exposure to stress may yield blunted cortisol, along with heightened DHEA (Lam et al., 2019), perhaps indicating efforts to combat stress and related brain tissue damage, which would not be necessary in healthy people. This would then yield decreased cortisol/DHEA ratios in patients relative to controls and explain why elevated cortisol/DHEA corresponded to reduced brain volume in patients only. Thus, cortisol/DHEA may serve as a neurotoxicity marker related to brain volume loss such that elevated cortisol/DHEA ratios are harmful to the brains of patients with schizophrenia while such a relationship is not clearly identifiable in the healthy brain.

All things considered, our findings demonstrate that DHEA may help mediate brain vulnerability in mental illness and tissue volume loss associated with schizophrenia to a certain degree. Being as how our finding was unique to the patient group may suggest that DHEA's neuroprotective effects are heightened under stress-related conditions, which is supported by findings by Jin and colleagues of a negative correlation between cortisol/DHEA ratios and hippocampal volume in people with major depressive disorder but not in controls (Jin et al., 2016). We did not find a significant relationship between serum cortisol levels and brain volume, which is consistent with some (Jin et al., 2016) but not all (Mondelli et al., 2010b) studies of mental illness. Between-study discrepancies may be attributed to study-specific differences in medication, serum collection and assay, imaging acquisition protocols and/or statistical methods. Similarly to previous work that reported a near-significant positive correlation between DHEA and hippocampal volume in their sample of depressed patients (Jin et al., 2016), we found a trend towards a significant positive correlation between DHEA and hippocampal volume in people with schizophrenia. However, in both studies, the ratio of cortisol/DHEA had stronger associations with brain volume than DHEA alone in patients. This supports the hypothesis that the ratio of cortisol to DHEA is more informative than their absolute concentrations alone (Wolkowitz et al., 2001), and that DHEA activity may be more influential in the hippocampus when interacting with cortisol activity. As the hippocampus and DLPFC are vulnerable targets of stress-related pathology (Sinclair et al., 2011; Webster et al., 2002) and reduced hippocampal volume has been exhibited in other disorders in which stress plays a role including post-traumatic stress disorder (Gurvits et al., 1996), Cushing's syndrome (Starkman et al., 1992) and depression (Sheline et al., 1999), identifying steroid markers that correspond with brain volumetric reduction may help us better understand the neurobiological basis for brain tissue loss across human disease.

Our study has some limitations. All patients in our sample were receiving antipsychotic medication. There is some evidence from animal models suggesting that clozapine is associated with decreases in DHEA (Nechmad et al., 2003). If this occurs in humans, then such an effect would lower DHEA levels in our patient sample; yet, we were still able to detect significantly elevated DHEA levels and we also did not find an association between circulating DHEA and CPZ equivalents. Additionally, the present study included measures of DHEA and not DHEA-sulfate, which should also be considered in future studies as they may differ in their circulating levels and relationship to symptomatology (Misiak et al., 2018; Strous et al., 2004). Lastly, DHEA is tightly linked with age such that concentrations markedly decrease around the early thirties (Sulcova et al., 1997). Our patient sample was nearly four years older on average than the control sample (mean ages were 35.7 vs 31.8 years, respectively), thus their DHEA levels may have started to decline for a longer period of time which could be a confounding factor in our analyses. However, despite the age difference, we found significantly increased DHEA levels in people with schizophrenia relative to the controls and we adjusted for age in all analyses involving hormones.

To conclude, this is the largest study to date to examine circulating levels of DHEA and cortisol/DHEA ratios in schizophrenia and the first study to link the cortisol/DHEA ratio with reduced brain volume in schizophrenia. Our findings add to the multiple lines of direct and indirect evidence supporting the intriguing phenomenon that a neuroprotective hormone, DHEA, is upregulated in some people with schizophrenia. Whether this truly serves as an effective compensatory mechanism has yet to be confirmed. Our findings also suggest that studying cortisol and DHEA in concert may serve as a potential

biomarker of stress-related brain tissue loss in people with schizophrenia. Altogether, these results further implicate the role of DHEA and HPA axis dysfunction in the pathophysiology of schizophrenia.

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Author contributions

EJ was involved in the conception of the project, analyzed the data and wrote and edited the manuscript. CSW was involved in the conception of the project, assisted with protocol and ethics construction, supervised the project in relation to data collection, management, monitoring and analysis, and edited the manuscript. TP, CW, DJH and RD coordinated and performed the blood assays and edited the manuscript. MOD performed the medical exams, assisted with recruitment and edited the manuscript. DL and RL performed and reviewed SCIDs, assisted with the recruitment, performed medical exams and edited the manuscript. CG supervised the Adelaide site, performed and reviewed SCIDs, assisted with recruitment, performed medical exams and edited the manuscript. TW was involved in the conception of the project, wrote and revised the protocol and ethics, coordinated the project, supervised the project in relation to data collection, management, monitoring and analysis, performed SCIDs and edited the manuscript.

Declaration of Competing Interest

The authors declare no conflict of interest in relation to this work.

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Appendix A. Supplementary data

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